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Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure

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Abstract

A systematic revision of the literature was conducted in order to undertake a comprehensive meta-analysis of all published observational studies on melanoma. An extensive analysis of the inconsistencies and variability in the estimates was performed to provide some clues about its Epidemiology. Following a systematic literature search, relative risks (RRs) for sun exposure were extracted from 57 studies published before September 2002. Intermittent sun exposure and sunburn history were shown to play considerable roles as risk factors for melanoma, whereas a high occupational sun exposure seemed to be inversely associated to melanoma. The country of study and adjustment of the estimates adjuste for phenotype and photo-type were significantly associated with the variability of the intermittent sun exposure estimates ($P = 0.024$, 0.003 and 0.030, respectively). For chronic sun exposure, inclusion of controls with dermatological diseases and latitude resulted in significantly different data ($P = 0.05$ and 0.031, respectively). Latitude was also shown to be important ($P = 0.031$) for a history of sunburn; studies conducted at higher latitudes presented higher risks for a history of sunburns. Role of country, inclusion of controls with dermatological diseases and other study features seemed to suggest that "well conducted" studies supported the intermittent sun exposure hypothesis: a positive association for intermittent sun exposure and an inverse association with a high continuous pattern of sun exposure.
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1. Introduction

Malignant melanoma of the skin (melanoma) is one of the few forms of cancer whose incidence and mortality rates are rising in many parts of the world where light-skinned populations live. The reasons for this increase are thought to be linked to changing sun exposure patterns, although many aspects of the aetiology of melanoma are not understood or are poorly quantified.

The present paper describes the results of a meta-analysis on the cutaneous melanoma risk and ultraviolet sun radiations, which was included in a wider project investigating all major risk factors for melanoma [1].

In 1991, the "Consensus Development Conference on Sunlight, Ultraviolet Radiation, and the Skin" stated that the only established exogenous causal factor for cutaneous melanoma in white populations is sun exposure [2]. Similar conclusions were reached by the

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International Association for Research on Cancer (IARC) [3], which has reviewed in great detail the relationship between melanoma and sun exposure and has accepted sun exposure as the main cause of cutaneous melanoma in humans. However, complete or more convincing answers to a number of questions on sun exposure are still needed. Such questions include whether the pattern of sun exposure is really important and acts independently of the amount of sun exposure and whether sunburn makes a specific contribution to the risk of skin cancer. It is often difficult to separate the interrelations between sunburn history, sun exposure habits, ability to tan and other phenotypic factors. Ultraviolet (UV) radiation may act as both an initiator through sunburn, for example, and a promoter, producing naevi and having promoting action on them, as well as a possible promoting action on other initiated melanocytes that do not proliferate at an early stage to form naevi [4].

Assessment of sun exposure has been investigated in this study looking at differences in patterns of sun exposure and the possible association with sunburns. Many studies showed positive associations between the melanoma risk and a history of sunburn, but a straightforward interpretation of this association is complicated. In fact, many studies consider sunburn a marker of acute sun exposure [5]. Furthermore, this inflammatory reaction may represent an increased risk for those with a high susceptibility rather than a direct effect of the presence of sunburn. Therefore, both questions, unusually intense sun exposure and skin sensitivity, must be considered in order to render the data meaningful.

Several publications have investigated sun exposure in association with melanoma, producing results that appear conflicting. In point of fact, they used different methods of information ascertainment and statistical analyses, and considered completely different populations. Furthermore, most of the evidence relevant to the effects of different patterns of sun exposure epidemiological studies and it is not easy to separate the effects of different patterns of exposure using epidemiological methods. Several methodological problems may bias the association between sunlight exposure and melanoma risk [6]. We have carried out an in-depth exploration of between-study heterogeneity and possible sources of bias searching for significant differences in study features, definitions adopted, characteristics of the populations and of the types of analyses conducted.

2. Patients and methods

2.1. Definition of outcome and exposures

The outcome of this systematic meta-analysis was histologically confirmed melanoma.

Sun exposure was classified as intermittent, chronic or total. Intermittent exposure indicated "an intermittent pattern of sun exposure" and it was generally assessed by posing questions about specific activities that would be likely to represent relatively severe intermittent exposure such as recreational activities: sunbathing, water sports, and vacations in sunny places. Chronic exposure indicated "a continuous or more continuous pattern of sun exposure" and it was measured essentially entirely as occupational exposure. Total exposure was evaluated as sun exposure of all kinds.

Sunburn is an inflammatory reaction that arises following acute exposure of the skin to intense solar radiation. Sunburn is considered by many authors [5,7,8] a biological marker of high dose of ultraviolet radiation penetrating to the melanocytes at the base of the epidermis, regardless of the degree of pigmentation in the epidermis.

In this paper, we refer to *Intermittent sun exposure* as the amount of intermittent pattern of sun exposure, to *Chronic sun exposure* as the amount of a more continuous pattern of sun exposure, to *Total sun exposure* as the amount of sun exposure of all kinds and to *Sunburns* as the number of episodes of sunburn. Where a study presented multiple measures for one or more of the four exposures categories, we chose the measure that covered exposure for the longest period of adult life. In cases where, for the chosen measure, there were more than two levels of exposure, we used the relative risk (RR) estimates for the highest level, in order to reduce the possibility of misclassification. When the decision about the most appropriate definition is not straightforward, the definition that presented the highest prevalence among controls was chosen. The choice of definitions, and of the corresponding risk estimates to be included, was evaluated in the sensitivity analysis by looking at the influence of single studies. The choice of which measure and which exposure to use was made independently of knowledge of the measure and level specific RR.

Between childhood exposure and adulthood exposure, the second option was chosen because there is evidence that self-reported childhood exposure is less reproducible than exposure at older ages [9]. This choice was checked in the heterogeneity analysis by looking at the relevance of the latent period considered and at the influence of age for sunburn history.

Thus, two further meta-analyses on sunburns in childhood and in adulthood were carried out. To assess sunburn in adulthood, it was decided to include studies with a clear indication that experiences occurred at an adult age (>19 years of age). "Childhood" was defined as considering subjects of no more than 15 years of age. Weinstock *et al.* [8] was not included in this sub group analysis because the age period considered was "15–20 years" and it was not coherent with the other definitions of childhood sunburns.

Those who do not suffer when lying in the sun are likely to spend more time doing so, therefore an analysis looking at sun exposure without adequate adjustment for the sun sensitivity factors, skin pigmentation and tendency to burn will underestimate the true relationship. Such adjusted measures were used instead of measures adjusted for factors that could themselves be related to sun exposure, such as the number of naevi. As was seen in the previous meta-analysis on naevi [1] the melanoma risk is strongly related to the number of naevi, which are increased in individuals with high levels of sun exposure. Thus, naevi may lie in the causal pathway between sun exposure and melanoma and in this case, the adjustment for naevi would not be appropriate because it would decrease the true association [10]. The mechanism for the association between sun exposure and melanoma may be related to the induction and/or transformation of naevi. In addition the number of naevi could be considered as a potential confounder. There is no consensus on this issue, but we decided to treat the number of naevi not as confounders, but as intermediates. The estimates adjusted for demographic factors, such as age and gender, and baseline characteristics, such as ethnic origin, skin pigmentation and inherent tendency to burn or tan easily, were favoured instead of measures adjusted for factors which themselves could be related to sun exposure, such as the number of naevi. In the sensitivity analysis, this choice has been evaluated. A heterogeneity analysis looking at the influence of adjustment was carried out on the fully adjusted estimates.

2.2. Data sources and search strategy

2.2.1. Selection of articles

Data searches and the search strategy were conducted on Medline (National Library of Medicine, Bethesda, USA) using the PubMed interrogation interface and EMBASE (Elsevier Science, Amsterdam, Holland) using OVID, as in the meta-analysis on naevi count. The reference lists of the retrieved articles and preceding reviews [11–18] on the topic were also checked. No language or time restrictions were applied.

Inclusion criteria were developed for the selection of all relevant articles, as described in the previous paper on naevi, including original independent papers that provided the necessary information to calculate the estimates.

Furthermore, it was essential that the populations studied were homogeneous, at least regarding the main risk factors for melanoma. Thus, studies did not include only cases of palms, plantar foot and vulva, since a distinct aetiology for such non sun-exposed sites is suggested [19]. Studies [20,21] conducted exclusively on young subjects (aged less than 19 years) with melanoma were excluded because they were few in number and melanoma in childhood is very rare. In addition, the mean age of the population in the other studies is around 50 years. Moreover, childhood melanoma very often arises in giant naevus with a different pathology. Children with *Xeroderma Pigmentosa* [22] have completely different risk factors, that are mainly genetic [20]. Chen *et al*. [23] was not included for the calculation of the main pooled estimates because it was not possible to extract an estimate that was not adjusted for naevi. A further pooled estimate that included fully adjusted estimates was calculated to evaluate this decision.

Inclusion and exclusion of single studies was evaluated in the sensitivity analysis to investigate their influence on the pooled results and to exclude potential biases. Wide inclusion criteria were chosen in order to start from the premise of using as much data as possible. This allowed us more data to investigate the possible heterogeneity, the key issue of this meta-analysis.

2.2.2. Extraction and unification of the data

A questionnaire was developed to collect all of the important information about each study, as described in the previous paper on naevi. Data on the definitions of different patterns of sun exposure, on latent periods, on the inclusion of controls with dermatological diseases, on percentages of subjects with fair phototype in cases and controls and data on latitude were also collected for this study. Studies conducted in several different populations at substantially different latitudes were not included in the heterogeneity analysis which evaluated latitude.

The distinction among the various measures of RR (e.g., odds ratio (OR), rate ratio and risk ratio) was ignored assuming that melanoma is a rare disease. Consequently, every measure of association was translated into log relative risk and corresponding variance with the formula proposed by Greenland in [24]. Where all the published estimates were adjusted for naevi, a crude estimate from published raw data was calculated. Statistical methods to extract the estimates from the articles were described in the previous paper on naevi.

Most results were for all subjects, combining the genders; some of them presented results separately for women and men with no combined data. They were used in that form, producing a number of independent datasets higher than the number of studies included in the meta-analysis.

2.2.3. Data analysis strategy

The summarised RR was estimated by pooling the study-specific estimates using the classical fixed effects and random effects models. The homogeneity of the effects across studies was assessed using the large sample test based on the χ^2 statistic [24,25]. As described in the previous paper on naevi, sub-group analyses and analysis of variance models were carried out to investigate

between-study heterogeneity. *P*-values, indicating the significance of factors investigated, were obtained with analysis of variance models. A sensitivity analysis was conducted to evaluate the inclusion criteria and influence of the individual studies. Publication bias was investigated by funnel-plot-based approaches to verify whether it might affect the validity of the estimates. *P*-values for the fit of the funnel plot in the sensitivity analysis published by Copas and Shi [26], *P*-values for the rank correlation test proposed by Begg (Spearman's ρ values) [27] and *P*-values for Egger's weighted-linear regression method are presented [28].

3. Results

3.1. Literature selection and study characteristics

Four hundred and thirty-eight articles were retrieved from MEDLINE. Of those, 83 articles were identified as potentially suitable for meta-analysis; of those, 57 were identified as fulfilling the inclusion criteria. An overview of the studies included in the selected group (for a total of 38.671 cases) is given in Table 1. Thirty-two studies were carried out in European countries, 19 in North America, 2 in Australia, 1 in New Zealand, 1 in Argentina, 1 in Brazil and 1 in Israel. We included 5 cohort studies (all dealing with chronic sun exposure), 51 case-control studies and 2 nested case-control studies.

For total sun exposure, 13 eligible independent case-control studies and 15 datasets were available. This was because Graham *et al.* [29] and Fears *et al.* [30] presented estimates separately for gender. Thirty-four independent studies provided information on the association between melanoma and intermittent exposure to UV radiations, in terms of a specific recreational or vacation exposure. Forty papers were identified concerning the association between melanoma and chronic sun exposure: 34 independent case-control studies, plus 1 nested case-control study and 5 cohort studies. Two of them (Osterlind *et al.* [31] and Pion *et al.* [32]) presented estimates separately for each gender. Thus, we arrived at 42 eligible independent datasets for chronic sun exposure. Thirty-four independent papers investigated the association between melanoma and sunburn. The datasets totalled 35 because Mackie *et al.* [33] presented estimates separately for gender.

3.2. Total sun exposure

ORs extracted from the included papers were plotted, with their confidence intervals (CIs) and weights (Fig. 1(a)). A random effects model was adopted because there was significant heterogeneity between the published estimates ($\chi^2 = 68.14$ with 14 degrees of freedom (d.f.)). The final pooled RR (RR = 1.34 with 95% CI:

Table 1
Features of the studies, on sun exposure and melanoma included in the meta-analysis

First author [Ref.]	Publication year	Country	Type study	*N* cases	*N* Controls	Source cases	Source controls	Total sun exp.	Intermittent Sun exp.	Chronic Sun exp.	Sunburn
Gellin GA. [54]	1969	USA	CC	79	1037	Hosp	Hosp	Yes		Yes	
Klepp O. [66]	1979	Norway	CC	78	131	Hosp	Hosp		Yes	Yes	
Lee JAH. [67]	1980	UK	Co	315		–	–			Yes	
Beral V. [39]	1981	UK	Co	1398		–	–			Yes	
MacKie RM. [68]	1982	Scotland	CC	113	113	Hosp	Hosp		Yes	Yes	Yes
Lew RA. [69]	1983	USA	CC	111	107	Hosp	Other		Yes		Yes
Cooke KR. [70]	1984	New Zealand	Co	501		–	–	–		Yes	
Elwood JM. [71]	1984	Canada	CC	595	595	Pop	Pop	Yes	Yes	Yes	Yes
Graham S. [48]	1985	USA	CC	404	521	Hosp	Hosp	Yes		Yes	
Green A. [72]	1985	Australia	CC	183	183	Pop	Pop	Yes	Yes		Yes
Elwood JM. [73]	1986	UK	CC	83	83	Hosp	Hosp			Yes	Yes
Holman CD. [57]	1986	Australia	CC	507	507	Pop	Pop	Yes	Yes	Yes	Yes
Vagero D. [74]	1986	Sweden	Co	4706	2630458[a]	–	–			Yes	
Bell CMJ. [75]	1987	UK	CC	268	1577	Hosp	Hosp		Yes	Yes	
Cristofolini M. [76]	1987	Italy	CC	103	205	Hosp	Hosp	Yes		Yes	Yes
Holly EA. [77]	1987	USA	CC	121	139	Hosp	Hosp				Yes

Osterlind A. [78]	1988	Denmark	CC	474	926	Pop	Pop		Yes	Yes	Yes
Garbe C. [79]	1989	Germany	CC	200	200	Hosp	Hosp			Yes	
MacKie RM. [80]	1989	UK	CC	280	280	Pop	Hosp				Yes
Weinstock MA. [81]	1989	USA	N CC	130	300	Pop	Pop				Yes
Beitner H. [82]	1990	Sweden	CC	523	505	Hosp	Pop		Yes	Yes	Yes
Dubin N. [83]	1990	USA	CC	289	527	Hosp	Hosp	Yes	Yes	Yes	Yes
Elwood JM. [84]	1990	UK	CC	195	195	Pop	Hosp				Yes
Grob JJ. [85]	1990	France	CC	207	295	Hosp	Pop	Yes	Yes	Yes	Yes
Weiss J. [86]	1991	Germany	CC	204	200	Hosp	Hosp		Yes	Yes	
Zaridze D. [87]	1992	Russia	CC	96	96	Hosp	Visit to h.		Yes		
Dunn-Lane J. [88]	1993	Ireland	CC	100	100	Hosp	Hosp		Yes	Yes	Yes
Herzfeld PM. [55]	1993	USA	CC	324	415	Pop	Pop		Yes	Yes	
Nelemans PI. [89]	1993	Netherlands	CC	141	183	Pop	Pop		Yes	Yes	Yes
Autier, P. [90]	1994	Belg, Fr, Germ	CC	420	447	Hosp	Neigh.		Yes	Yes	Yes
Pion IA. [91]	1994	USA	N CC	2799	8377	Pop	Pop			Yes	
Westerdahl J. [92]	1994	Sweden	CC	400	640	Pop	Pop		Yes	Yes	Yes
White E. [58]	1994	USA	CC	256	273	Pop	Pop	Yes		Yes	
Goodman KJ. [93]	1995	USA	CC	3527	53129	Pop	Pop			Yes	
Holly EA. [94]	1995	USA	CC	452	930	Pop	Pop		Yes	Yes	Yes
Chen YT. [95]	1996	USA	CC	548	494	Pop	Pop		Yes	Yes	Yes
Fritschi L. [96]	1996	Canada	CC	103	533	Pop	Pop		Yes		
Rodenas JM. [97]	1996	Spain	CC	105	138	Hosp	Visit to h.	Yes	Yes	Yes	Yes
Dabkowsk U. [98]	1997	Poland	CC	74	300	Hosp	Pop	Yes			Yes
Freedman DM. [99]	1997	USA	CC	12156	23845	Pop	Pop			Yes	
Moore DH. [100]	1997	USA	CC	69	69	Pop	Pop		Yes		Yes
Lock-Andersen J. [101]	1998	Denmark	CC	168	176	Hosp	Pop		Yes	Yes	
Wolf P. [102]	1998	Austria	CC	193	319	Hosp	Hosp		Yes	Yes	Yes
Zanetti R. [103]; Rosso, S. [104]	1992,98	Italy	CC	260	416	Pop	Pop		Yes	Yes	Yes
Carli P. [105]	1999	Italy	CC	131	174	Hosp	Pop		Yes	Yes	Yes
Tabenkin H. [106]	1999	Israel	CC	168	325	Pop	Pop		Yes	Yes	
Walter SD. [107]	1999	Canada	CC	583	608	Pop	Pop		Yes	Yes	
Mastrangelo G. [108]	2000	Italy	CC	99	104	Hosp	Pop		Yes		
Naldi L. [109]	2000	Italy	CC	542	538	Hosp	Hosp		Yes		Yes
Hakansson N. [110]	2001	Sweden	Co	525	323860[a]	–	–			Yes	
Kaskel P. [111]	2001	Germany	CC	271	271	Hosp	Hosp		Yes	Yes	Yes
Landi MT. [112]	2001	Italy	CC	183	179	Hosp	Pop+hosp		Yes	Yes	Yes
Loria D. [113]	2001	Argentina	CC	101	249	Hosp	Hosp		Yes	Yes	Yes
Pfahlberg A. [114]	2001	7 Europ countries	CC	603	627	Pop	Pop				Yes
Shors AR. [53]	2001	USA	CC	386	727	Pop	Pop	Yes			Yes
Bakos L. [115]	2002	Brasil	CC	103	206	Hosp	Hosp				Yes
Fears TR. [30]	2002	USA	CC	718	945	Hosp	Hosp	Yes			

[a] Cohort size: Pop, population; Hosp, hospital; CC, case-control; Co, Cohort; NCC, nested case-control. (1) Only one arm; (2) only back; Bel, Fr, Ger: Belgium, France and Germany; Visit to h.: visitors to hospitals; neigh., neighbours. Exp, exposure; USA, United States of America; UK, United Kingdom.

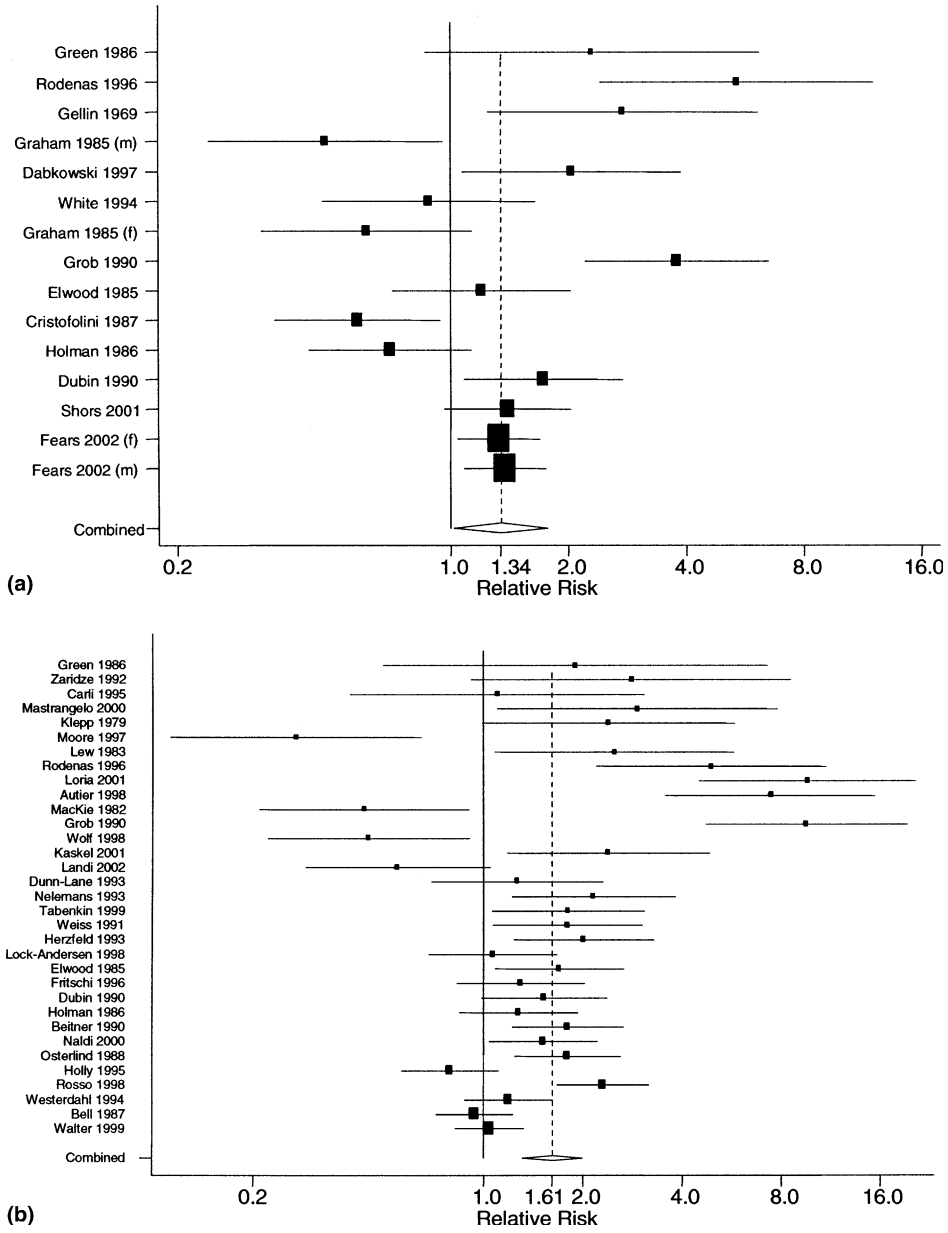
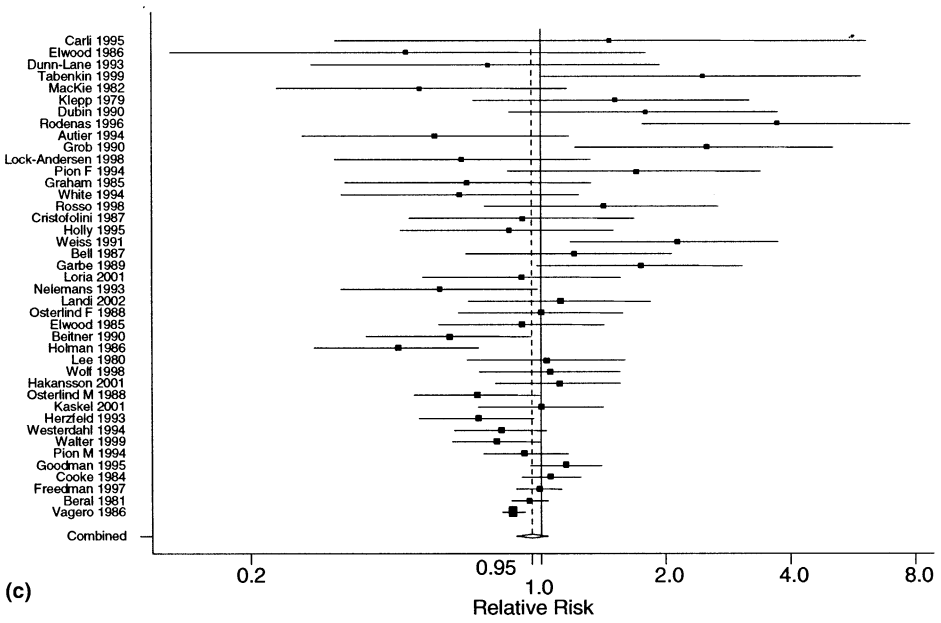


Fig. 1. (a) Relative risk (RR) estimates and 95% confidence intervals (CIs) for the melanoma risk and total sun exposure. (b) RR estimates and 95% CI for the melanoma risk and intermittent sun exposure. (c) RR estimates and 95% CIs for the melanoma risk and chronic sun exposure. (d) RR estimates and 95% CIs for the melanoma risk and sunburn history. (CIs were calculated using SE(log RR) estimated from published CI with the formula proposed by Greenland in [24].)

1.02, 1.77) suggested a slightly significant association between the total UV radiation and the risk of melanoma.

Looking at all possible factors that may have induced differences in outcomes, not due to sampling variation, sub-group analysis showed that heterogeneity within subgroups of studies remained significant. However, from meta-regression, it was seen that "publication year" significantly ($P = 0.05$) explained some of the between-study heterogeneity. From Fig. 2, it can be seen that studies published after 1990, showed an increased significant RR (RR=1.75 and 95% CI: 1.31; 2.35; $\chi = 26.62$, d.f. = 7 and $P < 0.001$); whereas studies published before 1990, indicated a lower risk (RR = 0.92 and 95% CI: 0.59; 1.42; $\chi = 20.77$, d.f. = 6 and $P = 0.002$) than the studies published later.

Regarding the type of study, it was seen that the eight studies with controls not drawn from hospitals showed higher and more precise values compared with studies with hospital-based controls. The pooled RR for studies with controls not drawn from hospitals indicated a slightly significant risk for total sun exposure (RR = 1.70; 95% CI: 1.07; 2.71; $\chi = 36.09$, d.f. = 7 and



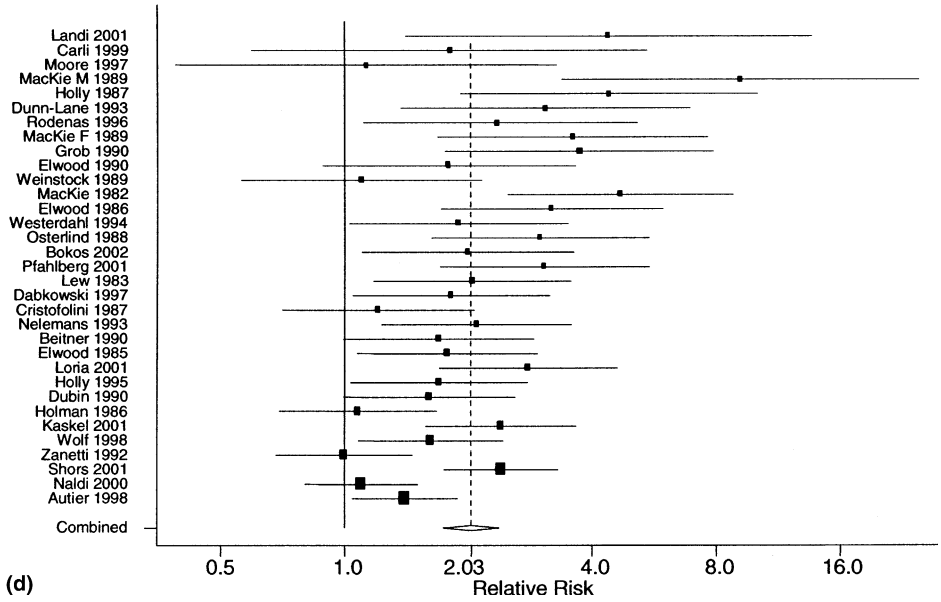


Fig. 1 (*continued*)

$P < 0.001$). In the subgroup of studies with hospital-based controls, the effect of total sun exposure disappeared completely (RR = 1.07 with 95% CI: 0.75, 1.53; $\chi = 28.58$, d.f. = 6 and $P < 0.001$).

The choice to exclude from the meta-analysis estimates adjusted for naevi was investigated and a new analysis was carried out including all RRs adjusted for the maximum number of confounders. The results (RR = 1.41 with 95% CI: 1.05, 1.88; $\chi = 62.59$, d.f. = 14 and $P < 0.001$) were quite similar to the final RR calculated on estimates not adjusted for naevi. Similarly, the inclusion of the papers [21,34] analysing melanoma in children did not change the final pooled estimate significantly (RR = 1.34 with 95% CI: 1.04, 1.73; $\chi = 68.39$, d.f. = 16 and $P < 0.001$).

Investigation of the funnel plot with Copas and Shi methods gave no indication of publication bias. Similar results were obtained with Begg's method ($P = 0.46$) and linear regression analysis on the funnel plot (Egger's method) ($P = 0.780$).

3.3. Intermitted sun exposure

Estimates included for the calculation of the final pooled RR were plotted in Fig. 1(b); as can be seen there was reasonably consistent evidence for a positive

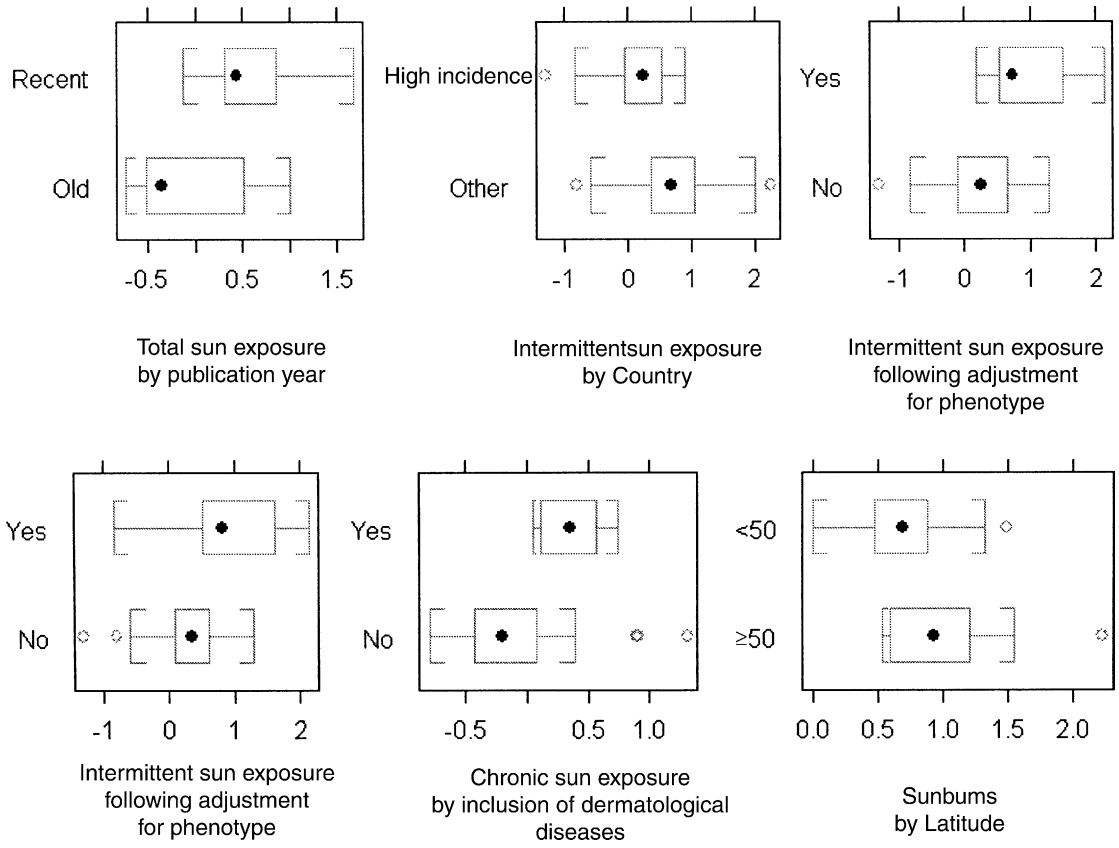


Fig. 2. Box and Whisker plots of Ln(RR) for Melanoma risk factors by heterogeneity factors. High incidence countries: Australia, USA, Canada or UK.

association between intermittent sun exposure and melanoma. The random effects model gave an indication of a significant risk: RR = 1.61 (95% CI: 1.31; 1.99).

A considerable between-study heterogeneity was found ($\chi^2 = 182.32$ with 32 d.f. and $P < 0.001$). The variation in ORs and RRs was likely to be related to many factors and it is probable that the considerable diversity among the definitions of intermittent sun exposure played an important role. Meta-regression indicated that factors related to "country" and "adjustment for phenotype and/or photo-type" were statistically significant ($P = 0.024$, 0.003 and 0.030, respectively) in explaining the between-study heterogeneity. Two-factor interactions were non-significant.

The pooled estimate (RR = 1.14, 95% CI: 0.90, 1.44, with $\chi^2 = 38.9$, d.f. = 12 $P < 0.001$) in the subgroup of studies coming from Australia, the United Sates of America (USA), Canada or the United Kingdom (UK) was significantly lower ($P = 0.024$; see Fig. 2) than the one obtained for the other countries (RR = 2.08, 95% CI: 1.55, 2.78, with $\chi^2 = 107.8$, d.f. = 19 and $P < 0.001$). The pooled RRs of the subgroups of estimates, adjusted for phenotype and phototype, indicated a significantly higher ($P = 0.003$ and 0.03 for phenotype and phototype, respectively) risk for intermittent sun exposure. Pooled RR of estimates adjusted for phenotype was 2.35 (95% CI: 1.78, 3.09) and for phototype was 2.35 (95% CI: 1.78, 3.09) and for phototype was 2.32 (95% CI: 1.55, 3.49). The pooled RRs of unadjusted estimates for phenotype and unadjusted estimates for phototype were much lower (RR = 1.18 with 95% CI: 0.94, 1.51 for phenotype and RR = 1.30 with 95% CI: 1.06, 1.61 for phototype; see Fig. 2).

As mentioned previously in the inclusion criteria section, Chen *et al.* [23], which published only estimates adjusted for naevi, was not included in the calculation of the main pooled estimate. A further pooled estimate that included all fully adjusted estimates was calculated to evaluate the influence of this adjustment. The pooled estimate was very close to the previous pooled RR (RR = 1.59 and 95% CI: 1.30, 1.93; $\chi = 167.13$, d.f. = 33 and $P < 0.001$).

Similarly, when we included the papers [21,34] analysing melanoma in children, the final pooled estimate did not change significantly (RR = 1.62 with 95% CI: 1.31, 1.99; $\chi = 182.40$, d.f. = 33 and $P < 0.001$).

Looking at the funnel plot, the Copas and Shi method gave no indication of publication bias for intermittent sun exposure. Similar results were obtained with Begg's method ($P = 0.183$) and linear regression analysis on the

funnel plot (Egger's method) ($P = 0.066$). The "Trim and fill" analysis suggested that the number of missing studies may be 6 and their inclusion would lead to a slightly lower pooled estimate (RR = 1.29; 95% CI: 1.03, 1.62).

3.4. Chronic sun exposure

ORs and RRs, with their CIs are plotted in Fig. 1(c). As can be seen, there were several studies that presented estimates lower than 1, indicating an inverse association with chronic sun exposure. However, the CIs very often included 1, showing a non-significant estimate. Even if there was a problem of heterogeneity ($\chi^2 = 96.06$, with 41 d.f. and $P < 0.001$), a general suggestion of a slight inverse association emerged from the analysis, but this was non-significant. The pooled RR, obtained from the random effects model, was: RR = 0.95 (95% CI: 0.87; 1.04).

Even if heterogeneity within subgroups remained significant, results from meta-regression indicated that two study features were statistically significant in explaining the variability between studies: these were "inclusion of controls with dermatological diseases" and "latitude". Two-factor interaction was non-significant.

In Fig. 2, a plot presents studies with the indication of inclusion of controls with dermatological diseases. As can be seen, the 6 studies, in which it was stated that these subjects had been included, all showed positive Ln(RR). The pooled RR of the 26 studies that did not include controls with dermatological diseases (RR = 0.87; 95% CI: 0.74, 1.02; $\chi^2 = 55.75$, d.f. = 25 and $P = 0.001$) was significantly ($P = 0.05$) lower than the RR of the studies that declared to have included them (RR = 1.29; 95% CI: 1.06, 1.57). For this latter sub-group of studies, the fixed effects model was used because there was no indication of significant heterogeneity ($\chi = 6.45$, d.f. = 5 and $P = 0.26$). Meta-regression indicated that another characteristic explaining variability among the estimates was latitude: at higher latitudes, we had a greater association between chronic sun exposure and melanoma ($P = 0.031$) (Fig. 3). Latitude was calculated for 32 of 42 studies by looking at the city, where the study was conducted, whereas for studies performed on whole regions, the average latitude was considered. The pooled RR of the 32 studies was similar to those calculated on whole group (RR = 0.98; 95% CI: 0.85,1.12).

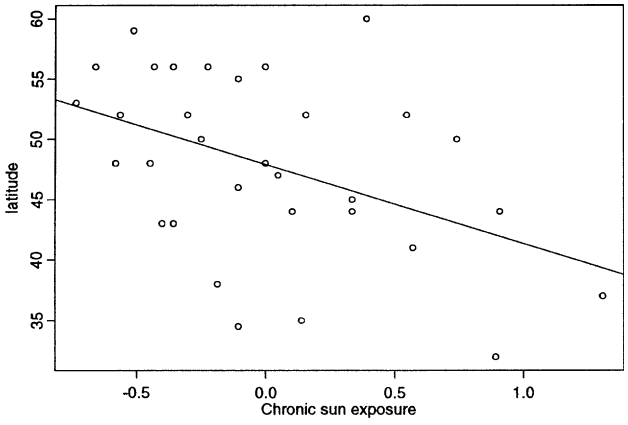


Fig. 3. Ln(RR) of chronic sun exposure by latitude.

There were some studies that presented different designs: Cooke *et al.* [35], Vagero *et al.* [36], Goodman *et al.* [37], Lee and Strickland [38], Beral and Robinson [39] and Freedman *et al.* [40]. Four of them also had big weights with a vast quantity of cases and controls. Goodman's paper [37] compared incidence cases of melanoma, recorded by population-based registries, to incidence cases of all other forms of registered cancers, with respect to declared occupation. Beral's [39] and Lee's [38] papers compared incidence cases and mortality of melanoma, respectively, recorded by population-based registries, to expected cases based on rates of the national employed population with exposure defined with the census (1971). Cooke's paper [35] compared observed and expected number of incidence cases for several occupational unit groups, in the New Zealand cancer registry. Freedman's paper [40] compared deaths from melanoma with non-cancer deaths, drawn from a database supported by two American national health institutes. Potential sunlight exposure was assessed by usual occupation recorded on the death certificate. Vagero's paper [36] presented an analysis based on incidence cases obtained from an extended Swedish cancer registry, created from a linkage of the Swedish Cancer Registry to the population census. For each case, census information, such as occupation was known. Their design was very different from the others and the information about sun exposure and inclusion of controls with problems was not particularly detailed; thus, a further analysis was conducted to investigate their influence on the results. After their exclusion, results were found to be very similar to the previous ones (RR = 0.96; 95% CI: 0.84, 1.09); the heterogeneity χ^2 test remained highly significant ($\chi = 82.12$, d.f. = 35 and $P < 0.001$).

The choice to exclude the estimates adjusted for naevi from the meta-analysis was evaluated and a new analysis was conducted including RRs adjusted for the maximum number of confounders, including naevi. The pooled RR on the fully adjusted estimates did not change significantly: RR = 0.96 (95% CI: 0.87, 1.04), with a highly significant between-study heterogeneity ($\chi = 109.51$, d.f. = 41 and $P < 0.001$).

No indication of publication bias was found.

3.5. Sunburn history

Estimates, included for the calculation of the final pooled RR, were plotted in Fig. 1(d). All of the estimates (except for Zanetti *et al.* [103], which was close

to 1) were greater than 1 indicating sunburn history as an important risk factor. Even if the lowest limits of the CIs were not all above 1, there was reasonable consistent evidence for a positive association between sunburns and melanoma. The random effects model gave an indication of a highly significant effect (RR = 2.03; 95% CI: 1.73, 2.37).

Between-study heterogeneity was highly significant ($\chi^2 = 84.83$ with d.f. = 32 and $P < 0.001$). Meta-regression indicated that characteristics explaining variability among the estimates were latitude and percentage of fair-skinned people in controls: at higher latitudes and also in studies where the percentage of fair-skinned people in controls was higher, there was a greater association between sunburns and melanoma. Studies carried out in countries at latitudes of 50 and above presented higher risk for sunburns than the ones conducted in countries at latitudes below 50 (Fig. 2, $P = 0.036$). The overall average latitude was 46 (standard error (SE) = 1.6). The pooled estimates were much higher for the studies at higher latitudes (RR = 2.54; 95% CI: 1.99, 3.24; $\chi = 19.51$ with d.f. = 11 and $P = 0.05$) suggesting a higher risk for melanoma due to sunburns. However, for the studies carried out at lower latitudes, the pooled estimate still indicated a significant association between melanoma and sunburns (RR = 1.91; 95% CI: 1.58, 2.31; with $\chi = 34.61$, d.f. = 16 and $P = 0.004$). Consistently, in the 22 studies where it was possible to calculate the percentage of fair-skinned people in the controls, we observed a positive association with melanoma risk by sunburns (meta-regression model: $\beta = 0.01$, SE = 0.005, P-value = 0.067).

As lentigo maligna melanoma is strongly associated with chronic sun exposure, and acral lentiginous melanoma occurs on non-sun-exposed sites, their inclusion could modify the risk estimates for intermittent sun exposure and sunburns [42]. When we studied the χ^2 tests for the sub group of studies, which did not include acral or lentigo melanomas, we could see that the heterogeneity analysis was no longer significant ($\chi^2 = 10.32$ with d.f. = 6 and $P = 0.11$). However, the pooled RR was very similar to the previous overall pooled estimate (RR = 2.21 95% CI: 1.59; 3.08). Looking at other features, typical of well conducted studies, we could observe that in the sub-group of studies that used blinding for the interviewers, the χ^2 test was no longer significant ($\chi^2 = 11.24$ with d.f. = 10 and $P = 0.34$) and the pooled RR was still highly significant (RR = 1.79 95% CI: 1.50; 2.11). As could be seen for these subgroups of studies, the pooled estimates were significantly greater than one, suggesting a significant positive association with melanoma, and there was no indication of heterogeneity. These considerations confirmed sunburn history as an important risk factor and suggest that blinding and histological type may be important study characteristics influencing the variability of the results.

Two studies are worth noting MacKie *et al.* [33], which presented a very high-risk estimate (for men RR = 9.30 95%; CI: 2.39; 24.95), and Autier and Dore [43], which showed a considerable weight ($w = 46$). A further meta-analysis was carried out without the data from MacKie (males estimates) and Autier, but there was no considerable reduction in the between-study heterogeneity ($\chi = 71.4$ with 30 d.f. and $P < 0.001$) and the final risk estimate did not change significantly: pooled RR = 2.00 with 95% CI (1.71; 2.35).

When the fully adjusted estimates were considered, Chen *et al.* [23] and Green *et al.* [44], which presented estimates adjusted for naevi, were included in the analysis. The pooled RR was lower, but not appreciably different from that obtained in the main analysis (RR = 1.80; 95% CI: 1.57; 2.07; $\chi^2 = 71.52$ with 34 d.f. and $P < 0.001$). Once more, with the inclusion of the 2 studies [21,34] analysing melanoma in children, the final pooled estimate did not change considerably (RR = 2.02; 95% CI: 1.73–2.34; $\chi = 84.85$, 34 d.f. and $P < 0.001$).

For sunburn in childhood, even if the χ^2 test showed significant between-study heterogeneity ($\chi^2 = 72.75$, d.f. = 18 and $P < 0.001$), there was convincing consistent evidence for a positive association with melanoma. The random effects model gave an indication of a significant risk: RR = 2.24 (95% CI: 1.73; 2.89). The 17 studies that showed RRs for events in adults suggested a slight reduction in the risk compared with sunburn in children (RR = 1.92 95%; CI: 1.55; 2.37; with $\chi = 35.81$, d.f. = 16 and $P = 0.003$). We also calculated a further pooled RR considering the 19 studies that presented an estimate for sunburns in "all life" and we found an intermediate value (RR = 2.08 95%; CI: 1.70; 2.55; with $\chi = 45.11$, d.f. = 18 and $P = 0.001$).

To conduct an evaluation of the influence of age on more comparable estimates, a further analysis was carried out using 15 studies that published both estimates, in childhood and adulthood. In 9 of the 15 studies, the estimates were higher in childhood than in adulthood. The pooled RR for sunburns in childhood was slightly higher than the pooled RR for sunburns in adulthood (RR = 1.99, 95% CI: 1.45; 2.74, with $\chi = 52.39$, d.f. = 14 and $P < 0.001$ and RR = 1.53, 95% CI: 1.26; 1.86, with $\chi = 28.68$, d.f. = 14 and $P = 0.01$, for childhood and adulthood, respectively), but meta-regression showed a non-significant difference among the estimates of the two groups ($P = 0.182$).

The funnel plot showed a clear asymmetry that suggested a possible problem of publication bias for the main analysis on sunburns. Rank correlation analysis (Begg's method) of the funnel plot, indicated that smaller studies tended to report a greater RR than larger studies ($P = 0.002$). Similarly, linear regression analysis (Egger's method) also indicated a general trend towards asymmetry of the funnel plot ($P = 0.001$). The "Trim

and fill'' analysis suggested that the number of missing studies may be 8 and their inclusion would lead to a slightly lower pooled estimate (RR = 1.73; 95% CI: 1.47, 2.04). Investigating publication bias with the sensitivity analysis proposed by Copas and Shi [45], a quite strong positive trend in the funnel plot was found ($P = 0.001$). This suggested that the main pooled estimate calculated at the beginning was probably too high. However, the precision of the studies was sufficiently strong for the overall evidence of a positive increase in risk, and even if we had considered 21 unpublished studies, the pooled RR remained significant: 1.55 (with 95% CI: 1.31; 1.83). When we evaluated the funnel plot analysing the studies grouped by latitude, the indication of publication bias was not so strong: for studies carried out at lower latitudes, the *P*-value for the funnel plot was 0.08. At higher latitudes, the sensitivity analysis proposed by Copas and Shi showed that, with 5 unpublished studies added, the indication of publication bias disappeared, but the pooled estimate was not considerably changed: RR = 2.18 (with 95% CI: 1.61; 2.95).

4. Discussion

The measurement of sun exposure represents a particular challenge as methods of recording and coding vary considerably between studies. No objective approach could be found for the evaluation of different patterns of exposure, and for the categorisation of levels of exposure. No consistency could be established, even on the use of particular reference groups. Inadequate definitions resulted in non-differential misclassification and this may modify the results. Several measures of total, intermittent and chronic sun exposure were used in the publications, including a variety of definitions, measured with questionnaires, concerning all life or shorter periods. Some of them used quite good classifications with sun exposure indexes, or accurate calculations of the total number of hours of exposure or the number of hours per day, whereas others used only broad categories.

For melanoma, the pattern of sun exposure several decades before diagnosis is probably an important factor [14], but this would be difficult to ascertain in a retrospective study. The lack of cohort studies is related to the fact that melanoma is in absolute terms a rare disease, and that sun exposure was not systematically recorded in any existing database, in the way, for example, medical doctors may record drug use. In fact, in the few nested case-control studies, data on sun exposure were very limited. By contrast, major case-control studies were characterised by good study designs by counting all the newly incident melanoma cases in the defined populations, completing interview data on a large proportion of cases and controls, and by using detailed interview techniques. However, these types of studies have the major disadvantage that the information collected concerned events which have occurred in the past. Retrospective assessment of sun exposure implies there is the potential for significant recall bias: if patients with melanoma or the interviewers are aware that sunlight might be associated with the disease, it is more likely that sun exposure will be reported [46]. In fact, in total sun exposure, the problem of recall bias may be one of the factors influencing the estimates inducing a significant difference between estimates published before and after 1990. In studies conducted before the 1990s, when most professional opinion was against the concept that melanoma could be related to sun exposure [47], the problem of recall bias was likely less considerable because at that time there was little public knowledge about the dangers of sun exposure. The acceptance of sun exposure as a danger, something regularly commented upon in the press, came later. Poorer quality exposure measures of the earlier studies could not be considered a reason for this difference by publication year because definitions used in the older studies were also quite good [48–50].

Another crucial aspect of case-control studies is the selection of representative controls. Response rates in studies with population-based controls have, in general, been adequate. Comparisons with the source population gave good evidence of comparability between the selected controls and their source populations, for general demographic features [51]. However, it is unlikely that controls recruited from the inpatients of various hospital departments would be representative of the cases, and thus results may be potentially biased [6]. Controls with diseases may be more aware of the effect of UV radiation and may more easily remember episodes of sun exposure. Thus, for total sun exposure, differences by type of case-controls study may be due to recall bias. In fact, four out of seven estimates obtained from studies with hospital- based controls came from studies that included controls with dermatological diseases or any tumours [29,52–54]. Furthermore, assessment of exposure by questionnaire in a way which will allow different types of exposure to be separated is difficult and requires that an interview lasting between 30 and 90 min be conducted [51]. Thus, studies carried out in clinical situations, sometimes using short interviews by busy medical staff, result in data that may be less accurate [51].

Interesting observations arose from the heterogeneity analysis of the countries of the studies. Results were consistent with the intermittent sun exposure hypothesis: particularly irregular and intense exposure to sunlight significantly increased the risk of melanoma, while more regular (chronic) exposure was inversely associated with melanoma. In fact, the pooled estimate for intermittent sun exposure, in the subgroup of studies

coming from Australia, USA, Canada or UK, was significantly different (lower, but still significantly higher than one) compared with the estimate obtained for the other countries. In fact, many studies conducted in Australia, USA, Canada or UK had better study designs. In studies coming from these countries and analysing intermittent sun exposure, cases were more often population-based (62% compared for the other countries; $\chi^2 = 4.41$, d.f. = 1 and $P = 0.036$) and had larger mean numbers of cases (284 compared with 234, for the other countries) and controls (481 compared with a 310). Many case-controls studies on chronic sun exposure, conducted in Australia, USA, Canada or UK, were community-based (17 out of 27 studies) and most presented quite detailed information on sun exposure. When we considered the four population-based case-controls studies [55–58], which stated that controls with dermatological diseases had been excluded and which were carried out in these countries, the pooled RR presented a non-significant heterogeneity and suggested a significantly inverse association with high chronic sun exposure (pooled RR = 0.64, 95% CI: 0.51, 0.81, with $\chi^2 = 3.35$, d.f. = 3 and $P = 0.34$). Thus, the indication for an inverse association with high chronic sun exposure came from studies that presented a "well conducted" design. One of the reasons for this difference by country may be related to the fact that these countries presented quite high incidences of melanoma and for many years melanoma was a matter of concern. Professional opinion in these countries maintained that melanoma could be related to sun exposure and many studies were planned to investigate this association.

Very similar results were found by Nelemans *et al.* [6] (RR = 1.57 with 95% CI: 1.29, 1.91 for intermittent exposure; RR = 0.73 with 95% CI: 0.60, 0.89 for chronic sun exposure) and Elwood and Jopson [46] (RR = 1.71 with 95% CI: 1.54, 1.90 for intermittent exposure; RR = 0.86 with 95% CI: 0.77, 0.96 for chronic sun exposure) meta-analyses. Nelemans indicated the important function of an exploration of the sources of variation in a paper that showed the effect of "blinding" in studies evaluating intermittent exposure to sunlight. In studies without blinding, the effect was considerably greater and significant because differential recall of past exposures may have introduced bias. Furthermore, he found that the results from population-based studies clustered around one value, while the hospital-based studies showed a greater diversity of results.

Elwood arrived at similar conclusions in a review published in 1996 [47], where he found an agreement between Western Australia and Northern hemisphere studies in terms of a low risk of melanoma seen with heavy occupational sun exposure. In the very detailed study published in 1985 [59], Elwood suggested that the association with occupational exposure may be non-linear, with an increase in risk related to small amounts of occupational exposure and a decrease in risk with long continued heavy exposure. This mixed overall pattern may explain the inconsistent results arising from many other studies that did not assess chronic sun exposure in enough detail. Elwood [47] investigated the ratio of the RR estimates of intermittent sun exposure to occupational sun exposure and found that the ratios of intermittent to chronic exposure tended to be positive for the studies with control groups drawn from the community, or those studies with hospital control groups which excluded patients with skin diseases or other cancers. This finding suggested that in well-conducted studies, it is easier to find a clear distinction between the two estimates and a stronger inverse association with long continued chronic sun exposure, as we have found in our heterogeneity analysis.

To make a comparison between intermittent and chronic sun exposure on comparable estimates, a further analysis was performed on the 19 studies that published both estimates and a significantly ($P = 0.015$) higher risk was found for intermittent compared with chronic sun exposure (RR = 1.46; 95% CI: 1.19, 1.79 and RR = 1.09; 95%CI: 0.86, 1.37 for intermittent and chronic sun exposure, respectively). Differences in the results relating to different types of sun exposure argued against significant recall bias.

It is important to stress that it is unlikely that the inverse association with chronic sun exposure means that occupational sun exposure protects against melanoma and the occupational exposed person likely has a higher risk of melanoma than a person who has no exposure to the sun at all. The reference category for occupational sun exposure is low continuous pattern sun exposure, which will include people with high intermittent pattern sun exposure, as well as people with low sun exposure of any kind.

The complexity of the relationship between solar exposure and melanoma should not be surprising, as sun exposure has a wide range of effects on the skin [3]. In fact, the effects of UV exposure are modified by skin responses that attempt to protect the organism. Thus, the increased risk associated with intermittent exposure may be because such exposures occur on relatively unprotected skin, giving high transmission to the level of the melanocytes. Regular exposure on tanned and thickening skin may be more effectively blocked at the epidermal level [51]. High- dose first exposure to the sun after a prolonged period of sun avoidance will cause substantial damage to DNA in melanocytes, which have a relatively low baseline capacity for DNA repair and a low melanin content. Furthermore, karatinocytes severely damaged by UV radiation may be destroyed by apoptosis, whereas melanocytes that are similarly damaged are retained, at some risk of subsequent mutation [60].

Tanning ability is one of the pigmentary characteristics that, probably exerts a modification effect on the relationship between sun exposure measures and the risk of melanoma. In fact, results from heterogeneity analysis in intermittent sun exposure suggested that if we do not take into account phenotype and phototype for adjustment of the estimates we will obtain RRs that are lower not because of the sun effect, but probably because people with sensitive skin do not try to tan to the same extent.

A different effect exerted by the sun was found when latitude was studied, with a greater risk for sunburns and a greater inverse association for chronic sun exposure at higher latitudes. This finding may be explained taking into account that at higher latitudes the frequency of fair-skinned people is greater and intermittent sun exposure probably plays a special role in more easily inducing sunburn episodes. This is consistent with our results that in studies with a higher percentage of fair-skinned subjects among the controls, the association between melanoma and sunburns is stronger. Furthermore, several authors [41,44,61] considered sunburn history to be an important indicator of intermittent sunlight exposure and some suggested that the effects of intermittent sunlight exposure can be best studied in populations living at higher latitudes [62,63]. Elwood suggested that, for identical outdoor exposure patterns, an individual at higher latitudes, will receive a relatively higher amount of total ultraviolet dosage from the intermittent component of their outdoor exposure [64]. Thus, the intermittent sun exposure hypothesis, would seem to hold more robustly at higher latitudes.

The greater consistency of a positive association for sunburn, compared with that for intermittent exposures, may indicate a specific relationship of melanoma with sunburn *per se*, or it may be that sunburn is simply a more easily remembered measure of intermittent exposure to the sun [41,61]. A relationship between sunburns and intermittent sun exposure is also suggested by the association, that we found, between sunburn and latitude, but it is not known whether sunburn is simply an indicator of a highly intermittent pattern of exposure or whether it has some additional, independent effect on the risk of melanoma.

The choice to extract estimates comparing the highest with the lowest category of exposure was carried out in order to reduce misclassifications. This method of examining the associations addresses only the question of whether a difference in risk exists between extreme categories of exposure. An important point to consider is that a person is not likely to change their habits from that of the highest to that of the lowest percentile, and the present estimates are intended primarily to reflect the strength of an observed association – an important criterion of causality. One limitation of this approach is that it may attenuate the summary RRs because we pooled together estimates related to different percentiles. In fact, the RR generated by a study that partitions exposure into quintiles will generate a larger RR between the highest and the lowest categories of exposure than does a study that partitions according to tertiles.

In some studies, the researcher tried to look at the effect of sun exposure at different times in life, but no firm conclusions could be drawn, primarily because recorded sun exposure for an individual tended to be somewhat similar throughout their life. In fact, subjects tended to behave in the same way at each period of life and it is difficult to separate the effects of differences in sun exposure at different ages [51]. Thus, in this study, no significant difference was found between sunburns in adulthood and in childhood. However, this may represent an interesting aspect that is worthy of further investigation because migrant studies indicated that the risk of melanoma is much lower in subjects who arrived in a country such as Australia after the age of 15 years, whereas the risk in those who arrived at around age 5 years is similar to the risk of the native country [77].

Conflict of interest statement

The authors have no conflict of interest to disclose.

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